Biomedicine & Pharmacotherapy 141 (2021) 111849

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Molecular mechanisms underlying curcumin-mediated microRNA regulation in carcinogenesis; Focused on gastrointestinal cancers

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ARTICLE INFO

Keywords:
Curcumin
Turmeric
Epigenetics
MicroRNA
Gastrointestinal cancers

ABSTRACT

Curcumin is a bioactive ingredient found in the Rhizomes of *Curcuma longa.* Curcumin is well known for its chemopreventive and anti-cancer properties. Recent findings have demonstrated several pharmacological and biological impacts of curcumin, related to the control and the management of gastrointestinal cancers. Mechanistically, curcumin exerts its biological impacts via antioxidant and anti-inflammatory effects through the interaction with various transcription factors and signaling molecules. Moreover, epigenetic modulators such as microRNAs (miRNAs) have been revealed as novel targets of curcumin. Curcumin was discovered to regulate the expression of numerous pathogenic miRNAs in gastric, colorectal, esophageal and liver cancers. The present systematic review was performed to identify miRNAs that are modulated by curcumin in gastrointestinal cancers.

1. Introduction

Malignant neoplasms originated from the gastrointestinal (GI) tract and related organs are the main indicator of cancer morbidity and mortality all over the world [1,2]. Despite recent advances in control, management and individualized therapies, clinical findings for the majority of GI are still unclear [3,4].

Recently high polyphenol herbs with multi-functional actions seem to be very interesting in the prevention and management of malignancies [5]. Curcumin (1,7-bis(4-hidroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), is an important nontoxic [6] yellow pigment of Curcuma longa, which has several anti-oxidant and anti-inflammatory properties [7] (Fig. 1). curcumin is a diarylheptanoid, belonging to the group of curcuminoids, which are natural phenols responsible for turmeric's yellow color [8]. It is demonstrated that curcumin has been used to manage a variety of oxidative stress-related conditions and chronic diseases [9]. Curcumin, has been shown to be a strong antitumor agent [10]. So far, there is lot of evidence demonstrated that curcumin has an apoptotic and anti-tumor function in cancer cells, although, it is known that it also suppresses metastatic spread and prevents cancer cell proliferation too [11].

Curcumin exhibits its beneficial effects on inflammation and oxidative stress in various ways; it was shown to suppress the generation of different type of cytokines, such as TNF-α and IL-1β [12]; curcumin has been shown to scavenge ROS through its original antioxidant function and increasing antioxidant response [13]; curcumin also has been shown to modulate several transcriptional and translational factors that affect oxidative stress and oxidant defense enzymes [14–16]. Recently it has been shown that curcumin may exert its effects through affecting several types of microRNAs (miRNAs) [17,18].

MiRNAs, a key component of the non-coding RNA family [19,20], play multiple cellular functions such as cell growth and proliferation, cell cycle, differentiation, programmed cell death (apoptosis), and tissue development [21–23]. MiRNA in humans and so many other living organisms has varying genomic backgrounds, which include intragenic and intergenic non-coding RNA sequences in introns or some situations within an exon of the gene [24]. Mature miRNA biogenesis begins with

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https://doi.org/10.1016/j.biopha.2021.111849
Received 19 March 2021; Received in revised form 8 June 2021; Accepted 24 June 2021
Available online 30 June 2021

Nomenclature

STAT3	Signal transducer and activator of transcription 3
AGO2	Argonaute RISC Catalytic Component 2
Bcl-2	B-cell lymphoma 2
BAX	Bcl-2-associated X protein
CDK4	Cyclin Dependent Kinase 4
PTEN	Phosphatase and tensin homolog
Akt	Protein kinase B
mTOR	mechanistic target of rapamycin
PI3K	Phosphoinositide 3-kinase
MAPK	Mitogen-activated protein kinase
MDA	Malondialdehyde
SOD	Superoxide dismutase
GPx	Glutathione peroxidase
CAT	Catalase
CRC	Colorectal cancer
PDCD4	Programmed Cell Death 4
CDF	curcumin-difluorinated
ROS	reactive Oxygen Species
ZBTB4	Zinc Finger And BTB Domain Containing 4
ZBTB10	Zinc Finger And BTB Domain Containing 10
HCC	Hepatocellular cancer
CD40	Cluster of differentiation 40
SP1	Specificity protein 1
KLF4	Kruppel-like factor 4
PDGF	platelet-derived growth factor
C/EBPα	CCAAT-enhancer-binding proteins
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
EZH2	Enhancer of zeste homolog 2
SET8	DNA methyltransferase
MTA1	metastasis-associated gene 1

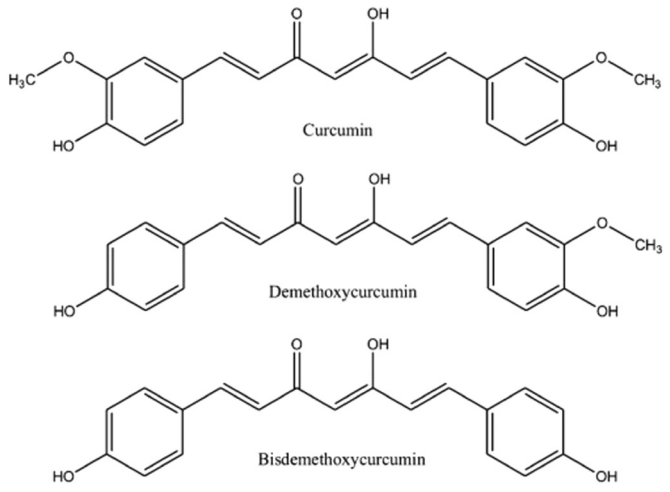

Fig. 1. Curcumin is a bright yellow chemical produced by Curcuma longa plants. It is the principal curcuminoid of turmeric (Curcuma longa), a member of the ginger family, Zingiberaceae. Chemically, curcumin is a diarylheptanoid, belonging to the group of curcuminoids, which are natural phenols responsible for turmeric's yellow color.

RNA polymerase II function of long non–protein sequence coding RNA primary transcripts, called precursor miRNAs [21,25]. These sequences are further modified by DROSHA and its linking partners (e.g., DGCR8) cause to primary miRNAs (pri-miRNA). Afterward, pri-miRNAs are moved into the cytoplasm through exportin 5; they intricate to DICER and RNA-induced silencing complex (RISC), which contains argonaute complexes. In cohesion with RISC, a leading strand helps to guide the mature miRNAs to the target mRNA, in consequence leading to down-regulation of target genes (Fig. 2). MiRNA biogenesis process is a tightly regulated procedure. Demodulation of miRNAs caused by the change in the pathway proteins biogenesis, such as DROSHA, DICER, and AGO2 could happen in cancer cells [26,27]. These changes could be as a consequence of either biogenesis faults under the impacts of hypoxia [28,29] or miRNA transcriptional alterations [30,31]. Despite biogenesis faults and systemic downregulation in miRNAs [26,29,32–34], several oncogenic miRNAs remarkably enhance in cancer cells [34–36]. Mechanisms by which the expression of oncogenic miRNAs increases in cancer cells are different and specific miRNA–dependent [37–39]. However, the effect of curcumin on cancers through miRNAs was evaluated before [40–42], but we want to focus on gastrointestinal cancers, so we summarized recent advances in understanding the complex interplay between miRNA regulations which is mediated by curcumin by a particular focus on gastrointestinal cancers.

2. Search strategy

A systematic electronic database search was conducted in Medline (http://www.ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com) and Google Scholar (http://scholar.google.com) without any language limitation, to find all published studies related to the impacts of curcumin on miRNAs. The search key terms included ["Curcumin OR Curcuma OR Curcuminoid OR Tumeric OR Zedoary zedoaria OR Longa OR Curcuma longa"] AND [Cancer OR malignancy OR Gastrointestinal Cancer OR esophageal cancer OR gastric cancer OR pancreatic cancer OR liver cancer OR small bowel cancer OR colon cancer OR rectal cancer] AND [MicroRNA OR MiRNA OR noun-coding RNA] in titles and abstracts. The search was conducted from inception to August 1, 2020. The primary database search yielded 255 records. After careful evaluation of titles and abstracts, 20 articles were selected and assessed in full text. After excluding duplicate and non-original documents, 11 articles were found eligible for the final review.

3. Effect of curcumin on oxidative stress through miRNAs

Dietary polyphenolic ingredients, including curcumin, have been involved in several biologic functions such as differentiation, development, proliferation, cellular stress, and oxidative stress signaling [43–45]. These pathways have been determined to be modulated by miRNAs [46,47]. Oxidative stress occurs when the amount of oxidant and ROS particles are greater than the potential of the antioxidant defense system of the host [48]. Reactive oxygen species (ROS), including hydroxyl radicals, superoxide anions, and hydrogen peroxide (H_2O_2) are easily produced under oxidative stress circumstances [49,50]. It has been shown that curcumin efficiently protects cells against H_2O_2 induced oxidative stress damage [51]. Curcumin neutralized the H_2O_2 induced OS by reducing MDA concentration, upregulating gene expression of Mn-SOD, Cu/Zn-SOD, GPX-4 and GPX-1, and increasing CAT, SOD activity [52]. We found that curcumin alleviated H2O2 induced oxidative stress, intestinal epithelial barrier injury and mitochondrial damage.

Oxidative stress (OS) refers to the increased intracellular concentration of ROS due to increasing oxidant factors or a decrease in the antioxidant defense system potential of the body [53]. ROS are by-products of aerobic metabolism substances that include the hydroxyl radicals (OH·), hydrogen peroxide (H2O2), and superoxide anion (O2–)

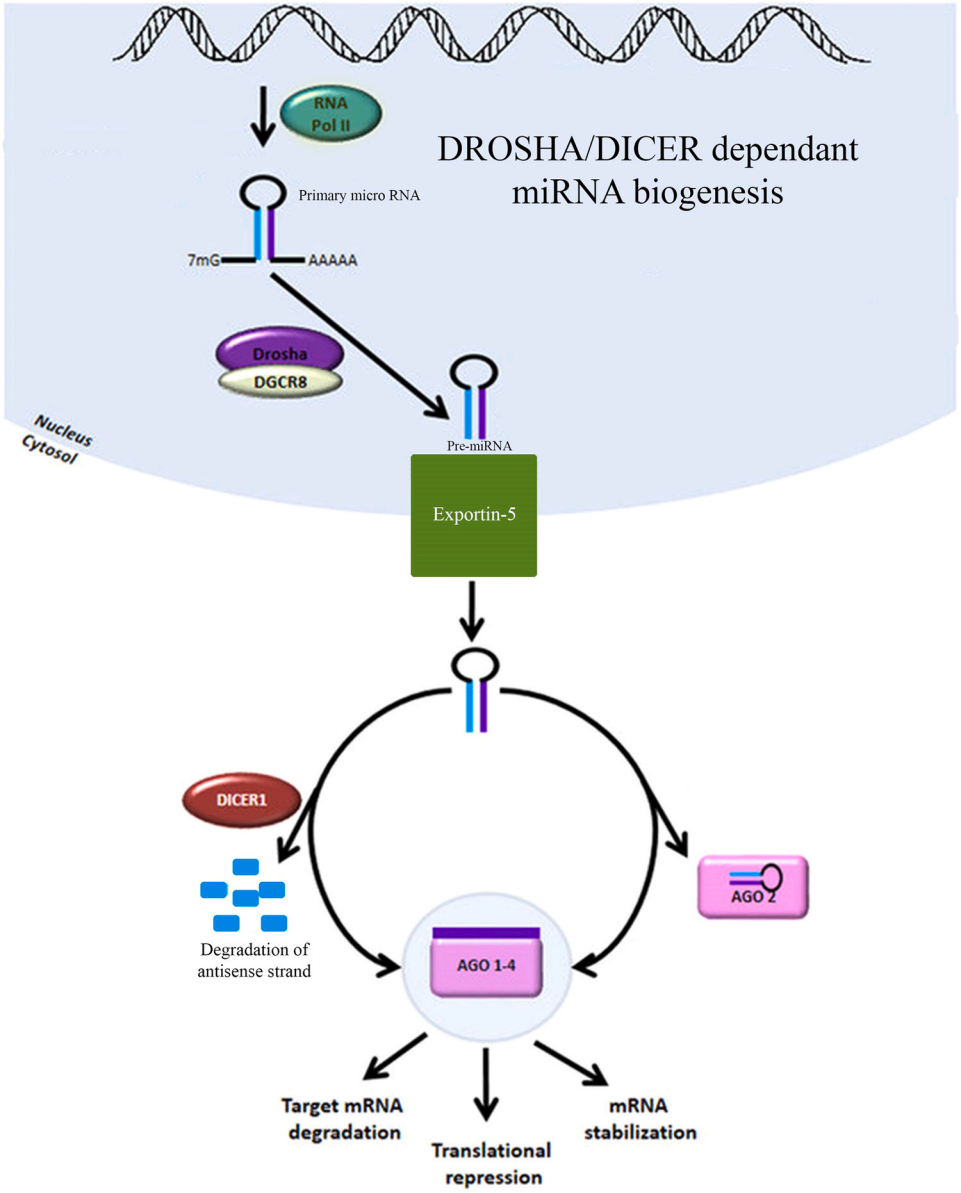

Fig. 2. MiRNA biogenesis and activity. The canonical miRNA biogenesis major pathway is Drosha- and Dicer-dependent. It begins with RNA Polymerase II-conducted transcription of miRNA genes. The pri-miRNA is metabolized in the nucleus by Drosha and DGCR8 to form pre-miRNA. The pre-miRNA is then exit from nucleus into the cytoplasm by Exportin-5. In the cytoplasm, pre-miRNA is further modified by the RNase III enzyme, Dicer. Integration with Dicer cause to degradation of the anti-sense strand of the miRNA duplex. The cytoplasmic pri-miRNA has been affected by AGO2, however the exact mechanism of miRNA maturation through this pathway still not clearly understood. Mature miRNA can function through three primary pathways: (1) destabilization and cleavage of target mRNA, (2) mRNA stabilization, and (3) translational repression.

[54]. ROS overload is often related to the oxidative stress, which induces the pathology of various chronic and acute diseases by damaging lipids, proteins, and DNA [55,56].

4. Effect of curcumin on cell survival and apoptosis through miRNAs

There is a growing of evidence proposing that various mechanisms are likely responsible for the multiple pharmacologic impacts of curcumin on anti-tumor-related pathways [57]. One of the mechanisms by which curcumin shows its anti-tumor function is apoptosis. Curcumin causes apoptosis in several types of cancers via multiple processes. For example, it leads to apoptosis in prostate cancer cells through iron chelation [58]. In melanoma cancer cells, it has been shown that generating ROS is another way that curcumin causes apoptosis [59]. It is also demonstrated that curcumin treatment significantly increases the sensitivity of lung cancer cells to Paclitaxel and decreases cell survival of cancer cells. It has revealed that curcumin could decrease the gene expression of MTA1 gene by upregulation of microRNA-30c in Paclitaxel-resistant lung cancer cells [60]. Also it has been demonstrated that curcumin decreases cell survival of cancer cells through its effect on inhibition of growth factors such as IGF-1 and insulin [61,62]. Recent outcomes suggest that curcumin can modulate Jak/STAT, NF-κB, jun, extracellular signal pathways in apoptosis through the regulation of specific miRNAs [17,41].

5. Curcumin and gastrointestinal cancers

As was mentioned above, curcumin possesses excellent anti-oxidant function. This pharmacological function is getting more attention in the field of gastrointestinal cancers [63]. In this field, for instance, colorectal cancer (CRC) is represented as one of the leading cause of mortality, even in developed communities. Diet and lifestyle changes are the main contributors to the development of CRC [64]. In recent years, attention towards consuming plant derived-natural ingredients in order to manage and treat gastrointestinal cancers has increased, and curcumin is one of these plant derived-natural compounds. We evaluated current evidence about the effect of curcumin on gastrointestinal cancers through its effects on miRNAs (Table 1).

Table 1
Effect of curcumin on various microRNAs in GI cancers.

Cancer	microRNAs	Effect of curcumin	Target gene/ transcription factor[a]	Biological function	Ref
Gastric	miR-34a	Up-regulation	CDK4, Bcl-2	↓Cell proliferation	[68]
	miR-33b	Up-regulation	XIAP	↑Apoptosis	[74]
	miR-21	Down-regulation	PTEN/Akt	↑Apoptosis	[76]
	miR-21	Down-regulation	PI3K/Akt/mTOR	↓Cell survival, ↓proliferation, and ↓migration	[75]
Colorectal	miR-21	Down-regulation	PI3K/Akt/mTOR	↓Cell survival, ↓proliferation, and ↓migration	[77]
	miR-27	Down-regulation	Pdcd4	↓Cell survival	[101]
	miR-34	Up-regulation	EMT	↓Chemoresistant	[104]
	miR-20a, miR-27a, and miR-17	Down-regulation	ZBTB4, ZBTB10	↓Cell growth	[105]
Hepatocellular	miR-200a and miR-200b	Up-regulation	EMT	↓Metastasis, ↓chemotherapeutic resistance	[110]
	miR-29a and miR-185	Up-regulation	DNA (cytosine-5-)-methyltransferase 1, 3A and 3B	↑DNA methylation	[113]
Pancratic	miRNA-22	Up-regulation	SP1, KLF4, PDGF, C/EBPα and NF-κB	↓Cell proliferation and migration	[125]
	let-7 miRNAs	Up-regulation	EZH2	↓Cell proliferation and migration	[134–136]
	miR-200	Up-regulation	EZH2	↓Tumor development and metastasis	[139,140]
	miR-7	Up-regulation	SET8	↑Apoptosis	[142]
Esophageal	miR-21	Down-regulation	Pdcd4, Bcl2	↑Tumor suppression, ↑Apoptosis	[152]

[a] Abbreviations: Bcl-2: B-cell lymphoma 2, CDK4: Cyclin Dependent Kinase 4, PTEN: Phosphatase and tensin homolog, Akt: Protein kinase B, mTOR: mechanistic target of rapamycin, PI3K: Phosphoinositide 3-kinase, PDCD4: Programmed Cell Death 4, CDF: curcumin-difluorinated, ZBTB4: Zinc Finger And BTB Domain Containing 4, ZBTB10: Zinc Finger And BTB Domain Containing 10, SP1: Specificity protein 1, KLF4: Kruppel-like factor 4, PDGF: platelet-derived growth factor, C/EBPα: CCAAT-enhancer-binding proteins, EZH2: Enhancer of zeste homolog 2, SET8: DNA methyltransferase

5.1. Gastric cancer

Curcumin has several pharmacological activities such as antitumor, antioxidative, and so on. It has been shown that curcumin has a lipophilic structure that makes it possible for it to penetrate the cell membrane easily and induce apoptosis [65,66]. These results demonstrated that curcumin administration inhibited the proliferation and induced cell apoptosis in gastric cancer cells. It has been shown that Curcumin suppressed the proliferation of gastric cancer cells, through upregulating of miR-34a [67]. Also, it has been demonstrated that the effect of curcumin in the suppression of gastric cancer cell proliferation is performed through inhibiting the levels of CDK4, Bcl-2, suppressing the G0/G1-S phase of the cell cycle, and inhibiting cyclin D1 in gastric cancer cells. Cyclin D1 is one of the regulators of the cell cycle that regulate the transition of cells from G1 to S phase [68]. Previous studies have shown that all of these factors also can be modulated by miRNAs [69,70].

Curcumin has been demonstrated to have a pivotal role in suppressing the progression of gastric cancer via different pathways, such as downregulation of β-catenin and STAT3 [71] and the Bcl/Bax-caspase 8, 9-caspase 3 pathway [72,73]. However, the special and individual mechanisms of its suppression of gastric cancer are still not clearly understood. In terms of the future progression of practical management application involving curcumin, extensive additional investigates into the possible mechanisms are both urgent and crucial. It has been shown that, curcumin act as a suppressor in gastric cancer cells, and curcumin treatment causes to an enhanced expression of miR-33b and a decreased expression of X-linked inhibitor-of-apoptosis protein (XIAP). XIAP has been reported to potently suppress the enzymatic function of caspases at both the initiation phase (caspase-9) and the execution phase (caspase-3 and caspase-7) of apoptosis [74]. These findings showed the possible role of curcumin in modulating apoptosis through miR-33b and XIAP in GC.

Gastric cancer cells studies have also discovered that the expression of ingredients of the miR-21/PTEN/Akt pathway was interrupted by curcumin [75]. PI3K/Akt/mTOR is a typical pro-survival and anti-apoptotic cellular signal transduction pathway, which modulates and controls several physiology and pathophysiology functions, including cell survival, proliferation, and migration [76]. The Akt signaling pathway regularly plays an important role in the control and regulation of the growth and proliferation of gastric cancer cells [77]. Moreover, it has been shown that suppression of the Akt signaling cascade can remarkably increase the apoptosis of gastric cancer cells [78]. MiRNAs post-transcriptionally regulates gene expressions. Recent findings have demonstrated that miR-21 is usually upregulated and acts as an oncogene in different types of malignancies [79]. As one of the targets of miR-21, PTEN has been shown to dephosphorylate phosphatidylinositol-3,4,5-trisphosphate in cells and act as a tumor inhibitor through suppression of the Akt/protein kinase B signaling pathway. Previous investigation has shown that miR-21 is upregulated in gastric cancer cells and the miR-21/PTEN/Akt molecular pathway has a critical role in the development of gastric cancer [80]. It has been demonstrated that suppressors of miR-21 significantly inhibit migration, invasion, proliferation, and colony formation of gastric cancer cells [81]. A recent investigation in MGC-803 cells, indicated that curcumin administration suppressed miR-21 and p-Akt expression, while the results show that curcumin also can increase PTEN protein expression [75]. These results proposed that curcumin administration effectively suppressed the miR-21/PTEN/Akt molecular pathway. In addition, curcumin remarkably induced apoptosis and suppressed proliferation in MGC-803 cells. These findings indicate that curcumin exerts its anti-cancer impacts in gastric cancer by suppressing the miR-21/PTEN/Akt molecular pathway.

MAPKs are signaling components that have critical roles in cell differentiation, proliferation, migration and survival [82]. The function of MAPK pathway inherently increases in numerous malignancies, such as gastric cancer [83]. It has been shown that curcumin treatment can inhibit MAPK pathway [84]. There are several levels of biological cross-talking between the MAPK pathway and PI3K/AKT/mTOR pathway [85]. So, it seems that suppression of both pathways with curcumin might lead to a more efficient anti-tumor effect compared to the suppression effect on one of these pathways.

5.2. Colorectal cancer

Colorectal cancer (CRC) represents the third most diagnosed type of cancer worldwide with an increased incidence rate and high mortality. CRC initiation and development result from the cumulation over time of genetic alterations in colonic epithelium cells with epigenetic changes

well-known as remarkable factors to cancer progression. CRC "epigenome" assessment showed that approximately all CRC have aberrantly methylated genes and altered miRNA expression [86].

CRC cells frequently resist the apoptotic process leading to the pathogenesis and development of neoplastic complications [87]. Resisting cells against death acquires different strategies to restrict apoptotic pathways. The basic mechanism by which malignant tumors resist against apoptosis process refers to an imbalance between pro-apoptotic and anti-apoptotic molecules, the restricted function of caspase, or defected cell lysis receptor signaling [88,89]. In addition, dysregulation of miRNA and their mRNA targets lead to the initiation/progression of colon carcinogenesis as well as invasion, angiogenesis, and metastasis [90,91]. Michael et al. [92] reported a dramatic downregulation of miR-145 and miR-143 in CRC, suggesting a role of miRNAs in CRC pathogenesis. Other studies have demonstrated the downregulation of miR-21 and retrieve the expression of miR-34 family in CRC [93]. Therefore, miRNAs may have prognostic and diagnostic applications for CRC patients. MiRNAs might also show novel treatment targets for gene therapy in the management of CRC.

Conventional oncologic treatments including chemotherapy, by activating proapoptotic mechanisms, have the potential to eliminate cancer cells [94]. Unfortunately, most anticancer drugs lead to significant side effects on normal cells and tumor resistance [95]. In this context, the combination of natural or dietary agents and anticancer drugs is an emerging area of cancer research.

Curcumin, as a bioactive component, induces apoptosis in CRC through both intrinsic and extrinsic pathways [96,97]. In CRC cells, the administration of curcumin leads to an up-regulation of pro-apoptotic components of the Bcl-2 family with the release of cytochrome-c from the mitochondria by down-regulation of the antiapoptotic protein Bcl-2 and oligomerization of the Bax protein [98,99]. Furthermore, the modulation of miRNA expression by curcumin in cell lines has been reported as a mechanism promoting anticancer effects [100]. Several studies highlighted the inhibition of miR-21 and miR-27 expression, tumor growth, invasion, and metastasis of curcumin. Curcumin stabilizes its tumor suppressor target Pdcd4 in CRC cells as well [101]. Likewise, curcumin-difluorinated (CDF), a curcumin analog with higher bioavailability, down-regulates miR-21 expression in chemo-resistant CRC cells via restoring PTEN levels and decreasing Akt phosphorylation [102]. Besides to miR-21, curcumin and CDF retrieve the expression of miR-34 family which has been lost in CRC partly via demethylation of the respective promoters [93,103]. Curcumin-mediated chemosensitization to 5-FU also occurred by up-regulation of epithelial-mesenchymal transition (EMT)-suppressive miRNAs, including miR-34, further highlighting its potential therapeutic use as an adjunct in patients with chemoresistant advanced CRC [104]. In line with these findings, curcumin showed CRC growth inhibition by ROS induction and reduction of Sp family of transcription factors as well as their regulators (i.e., ZBTB4 and ZBTB10) through miR-20a, miR-27a, and miR-17 [105]. Therefore, curcumin is known to modulate the eradication of CRC cells, potentially exerting its anti-cancer effect by affecting various miRNA-mediated epigenetic mechanisms.

5.3. Hepatocellular cancer

Hepatocellular cancer (HCC) is a comparatively chemoresistant gastrointestinal cancer, and patients with HCC experience resistance to almost all chemotherapeutic agents [106]. However, there are several novel agents that have been reported in the management of HCC, such as curcumin. MiRNAs have a pivotal function in gene expression in healthy and malignant cells. The miR-200 family is found to be involved in suppressing EMT, which is the initial phase of metastasis [107,108]. However, miR-200 family was also well known to have a critical role in chemotherapeutic resistance [109]. It has been shown that curcumin treatment promotes apoptosis in HCC cells through upregulating of miR-200a or miR-200b expression [110].

The modulation of cancer-related gene expression by miRNAs through epigenetic regulation could be a notable aspect of miRNAs function [111]. MiRNAs can affect the epigenetic landscape of cells by modulating particular epigenetic regulators including DNA methyltransferases, histone deacetylases, and histone acetyltransferases [112]. It has been indicated that curcumin can affect some of these epigenetic factors through its effect on miRNAs. It has been revealed that curcumin treatment can cause overexpression of miR-29a and miR-185 and down-regulate the expression of DNA (cytosine-5-)-methyltransferase 1, 3A, and 3B, and subsequently elevate the expression of maternally expressed gene 3 in HCC via DNA hypomethylation [113].

5.4. Pancreatic cancer

Pancreatic cancer is determined as the 14th most prevalent cancer and the 7th cause of cancer death in the world [114]. Recent investigations suggest that miRNA expression alteration may be an important mechanism underlying the diagnosis, pathophysiology, and management of pancreatic cancer [115]. It is crucial to control growth factors in gastrointestinal complications[61]. In addition, it has been demonstrated previously that curcumin has strong growth-suppression and apoptotic impacts on pancreatic cancer *in vitro* and *in vivo* [116,117].

These impacts of curcumin may be conducted via any of the several ways that curcumin intervenes with cell signaling [118,119]. Microarray experiments demonstrated that curcumin treatment on pancreatic cancer cells up-regulated the expression of some miRNAs (such as miRNA-22) but down-regulated some others (such as miRNA199a) [120]. In addition, it has been shown that curcumin implements its impacts on the miR-590–3p/CD40 axis to perform a protective activity in damaged endothelial cells [121].

Changing the expression of miRNA-22 by transfecting its miRNA oligonucleotides modulated the expression of its downstream transcriptional factors such as SP1 [122]. Mechanistically, it has been shown that miR-22 suppresses vascular smooth muscle cell proliferation and migration by reducing the transcriptional factor SP1 [123]. It has been approved that transcriptional factor SP1 increases proliferation of cancer cells through binding to the Kruppel-like factor 4 (KLF4) promoter which enhances platelet-derived growth factor (PDGF)-BB-stimulated cells [124]. In addition, SP1 encodes other transcriptional factors of the ETS subfamily such as PU.1, which can regulate the transcription of particular genes through interrelating with other transcriptional factors including C/EBPα or NF-κB [125]. These results indicate that curcumin can decrease the proliferation and migration of cancer cells through miR-22/SP1 axis. And also it demonstrates that curcumin can affect inflammatory markers through immunomodulatory effects [126]. The effect of curcumin on inflammatory markers related to the immune system such as TNF-α and IL-6 has been shown in previous studies [127,128].

In addition to the effect of curcumin on miRNAs related to transcriptional factors, it has been demonstrated that curcumin can affect cancer cells through the impact on epigenetic factors [129]. The histone methyltransferase EZH2 is one of the main epigenetic modulators of cell proliferation, development, and cancer cells survival [130]. It has been reported that EZH2 expression is enhanced in several human cancers, such as highly aggressive pancreatic cancers[131]. Curcumin has been indicated that affects pancreatic cancer cells through modulating EZH2 expression [132]. Furthermore, it has been shown that the let-7 miRNAs family activity as strong tumor inhibitors has been observed to be decreased in neoplasms, which causes increased expression of Ras and c-Myc in tumor cells [133]. Moreover, the downregulation of let-7 family of microRNAs has been reported in pancreatic cancer [134,135]. There are several pieces of evidence which indicated that EZH2 inactivation led to the increased let-7 expression, and thus curcumin treatment increases expression of let-7 miRNAs family, which can decrease EZH2 activity in pancreatic cancer cells and tumors [136].

Several recent shreds of evidence also expressed that miR-200 acts as a strong tumor inhibitor, essentially by suppressing the adherence of epithelial-to-mesenchymal transition (EMT) phenotype in process of the progression and development of tumors [137,138]. It has been observed that miR-200 expression was decreased in many cancers such as pancreatic tumors, which is related to metastasis and tumor progression [139,140]. Recent studies also indicated that the suppression of EZH2 causes an enhancement in the expression of miR-200 in pancreatic tumors, which show that EZH2 may be responsible for the modulation of miR-200 and let-7 in cancer cells. In this regard, curcumin treatment could increase the expression of miR-200 and let-7, which would be greatly beneficial in suppressing tumor development and metastasis [136].

In addition, there several investigations demonstrated that miR-7 could function as a tumor inhibitor gene in different types of human cancers [141]. It has been reported that miR-7 suppressed cancer cells' metastasis and growth and also enhanced the vulnerability of drug-resistant tumors to chemotherapeutic agents [141]. Furthermore, curcumin treatment has been suggested to inhibit cancer cells growth, invasion, and development, and cause cell apoptosis, which is related to enhance gene expression of miR-7 which led to reduce in the expression of SET8, one of the main miR-7 target genes in pancreatic cancer cells [142].

5.5. Esophageal cancer

Esophageal is one of the sixth main causes of cancer mortality in developed countries [143]. Esophageal cancer is usually diagnosed at the very end stages, with less than 10% of 5-year survival [144]. The high rate of morbidity, mortality, and low response rates of current treatment methods have led to investigations for less harmful complementary and alternative remedies. It has been reported that curcumin induces apoptosis and suppresses proliferation in esophageal cancer [145,146].

These previous studies have shown that curcumin treatment inhibits the development of esophageal tumor colonies, suppresses esophagosphere formation, alleviates cell cycle arrest and increases apoptosis and also suppresses miRNA expression, and modulates cancer cells inhibitor miRNA expression [147]. It has been demonstrated that several miRNAs upregulated remarkably and particularly miR-21 is up-regulated about 12 fold in esophageal tumors [148]. It has been shown that miR-21 is overexpressed in several solid cancer cells and it is related to tumor development, low rate of survival, and decrease response to therapeutic agents [149,150]. Curcumin intervention was confirmed to significantly decrease miR-21 expression in several types of tumors and metastasis [101,151]. Recent findings in esophageal cancer cells indicated that multiple targets have been identified for miR-21. The miR-21 has been demonstrated to significantly decrease the expression of gene Pdcd4 which functions as a strong tumor suppressor [152]. In addition, miR-21 can suppress the apoptosis process in cancer cells by modulating Bcl2 expression [153]. Eventually, miR-21 have the capability to suppress gemcitabine-induced cell apoptosis through the PTEN and PI-3 kinase pathway [154]. It has been determined that curcumin affects the gene expression of these mentioned factors in esophageal tumors through suppression of miR-21 [147].

6. Conclusion

In conclusion, molecular mechanisms are underlying curcumin-mediated miRNA regulation in the carcinogenesis of gastrointestinal cancers. In this regard, this review provides mechanistic evidence that curcumin intervention can be effective in the management of gastrointestinal cancer through its effect on modulation of some oncogenic or suppressive miRNAs.

Conflict of interest statement

The authors report no declarations of interest.

Acknowledgment

This work was supported by Grant number 98-3-37-16378 from Iran University of Medical Sciences.

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